level. Some newly active rate controlled electrically based transdermal techniques including: iontophoresis, electroporation, ultrasound and photomechanical waves have been developed and commercialized for the delivery of troublesome therapeutic protein and peptide based macromolecular drugs. This study covers the development of different electrically based transdermal techniques for delivery of therapeutic protein and peptide based macromolecular drugs, current status and assesses the pros and cons of each technique and summarises the evidence-base of their drug delivery capabilities.

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Molecularly imprinted polymers: macromolecule recognition

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Molecular imprinting is a technique used to engineer synthetic antibody mimics by the polymerisation of so-called functional monomers and cross-linkers around a target (template) species. Following removal of the template from the polymer matrix, cavities remain which display both chemical and steric selectivity for the imprinted molecule. To date the imprinting of biologically relevant macromolecules has been somewhat unsuccessful due to the inherent complexity of imprinting such moieties in aqueous media. Unlike small, organic molecules that are typically employed as templates, macromolecular structures such as peptides and proteins can exist in a multitude of conformations which leads to the development of heterogeneous binding sites as opposed to the well defined cavities formed during the regular imprinting process. The proteins will denature in traditional imprinting environments due to the presence of organic solvents and elevated temperatures. Additionally, the size of these biomolecules means that removal from the polymer matrix and subsequent re-binding is often inefficient. As a consequence, molecular imprinting has yet to achieve its true potential as efficacious, robust, reliable and cost-effective alternatives to the currently used antibody-based recognition systems. Projects currently underway within our laboratories aim to utilise target-selective peptides, derived from a phage display library, as a high affinity 'functional monomers' in a hybrid peptide-polymer molecularly selective system. Targets include lipopolysaccharide (LPS), the major pathogenic determinant of Gram negative bacteria and prion protein which is believed to be the causative agent of a group of invariably fatal neurodegenerative diseases known as transmissible spongiform encephalopathies (TSEs). Work to date has focused on optimisation of surface chemistries. Bifunctionalised polystyrene resin and glass surfaces have been synthesised to facilitate the independent immobilisation of peptide moiety and an initiator species. Polymer growth from the surface has been monitored by Fourier transform infra-red spectroscopy and atomic force microscopy. Future work will involve optimising a number of polymerisation variables and incorporating the phage-display derived peptide into the system to fully evaluate its potential as an antibody mimic.

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Interference of mycobacterium tuberculosis with the endocytic pathways on macrophages and dendritic cells from healthy donors: role of cathepsins

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Antigen-presenting cells (APC) such as macrophages and dendritic cells (DCs) play a pivotal role in tuberculosis pathogenesis. Macrophages are also key effector cells in mycobacteria killing. In order to survive inside the host immune cells mycobacteria developed different strategies. Among them blocking of phagosome-lysosome fusion and consequential reduced phagosome acidification assumes a crucial role allowing mycobacteria to escape acidic pH and destruction by proteolytic enzymes present in phagolysosomes. Since phagosome acidification varies between macrophages and DCs this may allow different kinetics of acquisition and activity for the enzymes involved. The aim of the present study was to compare the distribution of two key cathepsins: the exopeptidase cathepsin B and the endopeptidase cathepsin S inside human monocyte derived macrophages and DCs infected with *Mycobacterium* spp. Infected immune cells were collected after 3 hours and 1 day post-infection and prepared either for immunofluorescence confocal microscopy or for immunogold electron microscopy on ultrathin cryo sections. In macrophages we did not observe significant co-localization between either BCG or Mycobacterium tuberculosis and cathepsins B or S indicating that phagosome-lysosome fusion was strongly hindered. Similar results were observed for Mycobacterium tuberculosis after infection of DCs. In DCs the acquisition of cathepsin B into the phagosomes containing BCG was different from the acquisition of cathepsin S. Cathepsin S content was decreased by 30% after 1 day of infection whereas cathepsin B content inside BCG-positive phagosomes was increased. Our data indicate that cathepsins might be involved in differential mycobacterial persistence in macrophages compared to dendritic cells.

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Role of mycobacterium tuberculosis outermembrane porins in bacterial survival within macrophages

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Mycobacterium tuberculosis (Mtb) is the etiologic agent of tuberculosis a major worldwide health concern. One important feature in Mtb virulence is the ability to withstand the detrimental conditions of the phagosome within macrophages. Most of the virulence factors of Mtb are PAMPS from the outer membrane of the bacilli. Outer membrane porins participate in the inflow of hydrophilic compounds and we have shown that they are important for mycobacteria intracellular survival. Several porins have already been described as a means for nutrient acquisition but also as a possible pathway for antibiotic inflow. Previous studies showed that mutant